Sex Differences in Healthy Aging and Mortality in Heterogeneous Stock (HS) Mice

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ABSTRACT
The sex paradox in mortality and morbidity has been a long-standing subject of interest among demographers. Research in complex systems such as human populations has uncovered many mechanisms that influence this paradox, including biological, social, and psychological factors but have been less successful in disentangling these mechanisms. Perspectives from laboratory animal models can provide insight into sex differences in the intersection between mortality and morbidity by controlling for environmental factors that may influence this outcome. In this study, we examine active life expectancy in a sample of 319 heterogeneous stock (HS) mice which are particularly useful in studying genetically heterogeneous groups such as human populations. We use multiple measures of activity assessed at 6 time points. We expect to find sex differences in active life expectancy of the HS mice, which represent biological differences in the progression of functional limitation in the aging process.

Background and Significance
Researchers in human biodemography have long puzzled about the apparent male-female health-survival paradox. Even in poor countries, women have longer life expectancies than men (Barford et al. 2006), but when comparing men and women on conventional measures of health—chronic disease, multi-morbidity, ADLs—women fare worse. In contrast, men consistently rate their health better than women (Olsen and Dahl 2007), perform better on strength tests, report fewer diseases, and experience fewer ADLs; nevertheless, they have higher death rates in all age groups when compared to women. Attempts to make sense of these differences have invoked biological, social and psychological explanations.

When studying human populations, solving this puzzle is complicated by the fact that people sort themselves into different circumstances, different roles, different relationships, and their participation in this social world has implications for their biological and psychological functioning. Equally important is that people are born into different endowment positions: households differ in economic resources; families may be functional or dysfunctional; children are differentially exposed to enriched or deprived environments. An important implication of these SES differences involves access to education, quality health care services, and nutritious diets. For all these reasons, trying to parse the social from the biological is fraught with difficulty.

Finally, the difficulty and expense of collecting biological and health data from human respondents is well documented. People must be tracked for longitudinal studies; attempts to secure measurements for a sizeable proportion of the lifespan requires decades of effort; attrition and refusals complicate the interpretation of findings; and standardizing the timing of data collection across respondents is difficult if not impossible for a sizeable sample.

Research based on animal models can provide another perspective on these issues—especially if genetically heterogeneous stocks are the model of choice. Although the general approach in using animal models has been to use a uniform genotype, relying on inbred strains, a genetically heterogeneous population can be systematically produced by intercrossing inbred strains. Using genetically heterogeneous stocks are particularly useful for the study of complex systems (McClearn and Hofer 1999). Previous analysis of the HS mice dataset revealed sex differences in mortality (Heller et al. 1998), with females having lower mortality than males in younger ages

but experienced mortality acceleration in later ages, resulting in a mortality crossover close to the mean age at death. Several activity factors and biomarker indicators were found to be significant in influencing these mortality patterns. In this paper, we extend the previous work by Heller et al. (1998) by employing a multistate life table approach to analyze sex differences in the progression of functional limitations in Heterogeneous Stock (HS) mice. In human models, this approach has been used to describe the intersection between mortality and morbidity at the population level (e.g. Crimmins et al. 1997).

Data

The heterogeneous mice stock used in this study were established by intercrossing 8 inbred strains: A, AKR, BALB/c, C3H/2, C57BL/6, DBA/2, Is, and RIII (McClearn et al. 1970). These animals were born and maintained in a barrier facility. The total sample consists of 319 mice. Mean age at death was 769 days for male mice and 772 days for female mice. The design involved longitudinal measurement of a parent and an offspring cohort of animals at 45, 90, 360, 630, 900 and 1170 days of age and cross-sectional samples at the same ages. The intervals were spaced to evaluate early developmental stages and then allow at least three measurements for most of the mice.

Measures in multiple domains were obtained, including activity, free radical mechanisms, and physiology, and the immune system. Six activity measures are based on three apparatuses: the number of crossings from one square to another (the floor of the cage is divided into 4 squares); the number of times the animal stands on its hind legs; the number of times the mouse inserts its nose into the floor holes (one centered in each of 4 squares); the number of seconds the mouse can stay on a wooden dowel (1.6 cm in diameter); average number of sectors entered while on the rod (5 sectors 17.8 cm long); average number of seconds the mouse hangs by its tail from a monofilament cord. These assessments are generally considered to be measures of strength, agility, coordination, curiosity and fear (among other things) in various combinations.

Methodology

We will calculate two types of life table models to assess the burden of disease among HS mice. First, we will calculate population-based life tables that identify the expected years of active and inactive life for mice of a given age by sex. These models will allow us to evaluate how sex, at the population level, is associated with disease burden. We also calculate functional status-based life table models to identify the implications of having major activity limitations at a given age on active life expectancy. Earlier onset of mobility or strength limitations may result in an expansion of morbidity, a pattern that occurs in human populations in the early stages of population aging with increasing social capacity for health (Hidajat et al. 2007).

The Markov-based life table models (Schoen 1988) rely on the calculation of transition rates. These transition rates estimate the mobility between health states, and from a health state to mortality, for mice of a given age and sex. Our two-state model of active life expectancy is bidirectional, which allows mice to decline or improve in health and estimates mortality as a state-dependent process. For the MSLT, we use a hazard model approach to estimate transition rates (Hayward and Grady 1990; Land et al. 1994), whereby the instantaneous transition rate, $\mu_{ij}(x)$, is the force of transition from state *i* to state *j*. The rate is defined as:

$$\mu_{ij}(x) = \lim_{\Delta x \to 0} \frac{p_{ij}(x, x+\Delta x)}{\Delta x} = \mu_{ijx}.$$

We assume that all disability events occur at the end of the time interval; we also assume that deaths occur in mid interval. The transition rate is constrained to equal the constant, $\mu_{ij}(x)$, for all individuals of a given age-- age x to x+n-- but it is allowed to vary across different ages, allowing us to fit a piece-wise exponential transition rate model. The estimated transition rates are based on changes in health states across the observational intervals in the study (at 45, 90, 360, 630, 900, and 1170 days). We estimate the rates using a log-linear modeling approach and then use these parameter estimates to calculate predicted age-specific transition rates, m*(x), for male and female mice, and the predicted rates serve as the inputs for the multistate life tables.

We are currently preparing the dataset for analysis. We first plan to perform factor analyses on the six activity measures to determine the conceptual groupings of activities. We then use the set of activity measures that best represent a single indicator of activity. We expect to complete this phase of analysis by December 2008. We then proceed with modeling transitions in and out of the 2 health states and calculations of the multistate life tables. We expect to complete analyses by early Spring 2009.

Conclusion

The sex difference in mortality and morbidity has been a longstanding interest in scientific studies. Research on human models have revealed a complex interplay of genetic, biological, and socio-cultural factors that influence the sex gap in mortality and morbidity. There has been a lively body of research in sex differences in longevity in animal models as well, but animal researchers oftentimes use smaller samples, have cross-sectional research designs, and restrict their samples to genetically homogeneous stocks. In this paper, we combine an approach oftentimes used in human models, namely the multistate life table method, and use a mice model to examine sex differences in healthy life expectancy. We use a heterogeneous stock of mice to simulate the genetic variation existing in human populations. We also use a longitudinal study design with repeated measures of functional activities. We hope to gain insight into sex differences in the process of decline in functional limitations from this model.

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